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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/653,294	05/24/96	CLAYBERGER C	286002020023

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1644	29

DATE MAILED: 08/16/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/653,294	Clayberger et al.
Examiner	**Group Art Unit**
Thomas Cunningham	1644

☒ Responsive to communication(s) filed on *Jun 3, 1999*.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-26* is/are pending in the application.

Of the above, claim(s) *22-26* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-21* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. Claims 1-21 are active. This action is responsive to the request for reconsideration mailed 6/1/99 (Paper No. 28).

2. Applicant's election of record of Group I, claims 1-21 with traverse is noted. Claims 22-26 were previously withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a nonelected invention.

3. (Maintained) Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for particular peptides such as the sequences demonstrated to inhibit cytolysis on pages 21-et seq. of the specification, does not reasonably provide enablement for all the peptides encompassed by broad claim language.

E. (maintained) Diverse peptides. Claims 1-21 read broadly on peptides comprising residues 75-84 of any HLA-B alpha chain. However, page 21, lines 27-29 indicate that only peptides having sequences corresponding to particular alleles of HLA-B alpha 1 block CTL lytic responses. E.g. HLA-B2702 blocks, but HLAB2705 does not. It would be unpredictable which peptide species would be capable of multiallele blocking without testing of different peptide species on a case-by-case basis. For instance, pages 21-22 of the specification disclose that the HLA-B2702.75-84 and HLA-B2705.75-84 peptides, though differing in only three residues (see lines 6-7 on page 21) have materially different effects: the HLA-B2702 peptide inhibited lysis; the HLA-B2705 peptide did not.

--The Applicant urges on page 3 of the request for reconsideration that the example cited in the rejection pertains to (a) monomers not the claimed dimers and (b) is directed to inhibition of CTL lysis not the claimed inhibition of lymphocyte proliferation. However, if the functional effects of substitution in the monomeric sequence are unpredictable, one would reasonably expect that they would be unpredictable for dimeric or other sequences of higher order as well because substitutions would be expected to alter the structure and binding residues of either a monomeric or dimeric product. Similarly one with skill in the art would recognize that each function of a molecule whether it be to induce CTL lysis or lymphocyte proliferation correlates with a structure contained within the active molecule. Therefore the effects of altering the structure of the recited dimeric products are unpredictable regardless of whether the functional property is inhibition of CTL lysis or lymphocyte proliferation. Applicant's attention is directed to Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016 (CAFC 1991):

> Patent applicant is entitled to claim invention generically, if invention is described sufficiently to meet requirements of 35 USC 112; however, applicant, in claims for

> DNA sequences encoding erythropoietin, which has claimed every possible analog of gene containing about 4,000 nucleotides, but which has provided details for preparing only few EPO analog genes has not provided sufficient disclosure to support its claims, since, in view of structural complexity of EPO gene, manifold possibilities for change in its structure, and uncertainty as to what utility will be possessed by these analogs, additional disclosure is needed as to identifying various analogs within scope of claim, methods for making them, and structural requirements for producing compounds with EPO-like activity.

While Amgen addresses the unpredictability of which DNA sequences would encode functional erythropoietin analogs, the same or similar issues of unpredictability of the functional characteristics of analogs of erythropoietin pertain to whether the claims in the instant application are enabled. The recited products meet two criteria--that they (a) inhibit lymphocyte proliferation and (b) contain a broad structural motif encompassing both homo- and heterodimers. However, the specification provides no guidance as to which of billions of different possible structural analogs would in fact inhibit lymphocyte proliferation.

F. (Maintained) Variants. Claims 1-21 also encompass variants of the recited (HLA-B derived) peptide sequences. It would be unpredictable which mutations of an HLA-B 75-84 sequence would retain the critical functional property of being able to inhibit CTL activity because such mutations would be expected to affect functional binding of the peptide to the T cell receptor or accessory molecules. Modifications to the recited peptides, whether the addition, substitution, or deletion of amino acid residues, or the joining of such peptides to other chemical moieties would be expected to have unexpected, unpredictable effects on the activity of the particular peptide to modulate CTL responses, see e.g. Bowie, et al., Science 247:1306-1310 (1990). It is unclear how the peptides are actually modulating CTL responses, but one with skill in the art would expect that the claimed peptide compounds are interfering with the T cell receptor (TCR) antigen presenting cell interaction. It is unclear on a structural basis which types of modifications can be made to a "blocking" or stimulatory peptide and still have it exert its functional effect. For instance a stimulatory peptide that had bulky, sterically hindering chemical moieties joined to it would not be expected to effectively stimulate CTL responses, because the additional moieties would be expected to prevent it from binding to the sites on the CTL or the APC necessary for inducing CTL stimulation. Each chemical modification of a peptide known to modulate CTL activity would have to be investigated on a case-by-case basis and thus would impose a burden of undue experimentation on one with skill in the art.

--See argument above.

H. (Withdrawn) Immunosuppressive agent required. According to page 31 of the specification

allograft survival was similar in control and peptide-treated groups. Only groups treated with CSA had significant increases in graft survival time.

--Applicant's arguments on page 4 of the last response and the claim language limitation obviate this issue.

J. (Merged into issue above) The compound of claim 1 appears to be a peptide homo- or heterodimer. One would expect that only certain types of dimeric compounds have the ability to reduce CTL responses because different configurations of dimers would have different structures or spacing of determinants, and therefore different functional abilities to compete or bind to T cell ligands or MHC Class I molecules. Since a particular mechanism of action for the peptide dimers has not been adequately described, it would be unpredictable which structures would retain functional activity.

--This issue is merged into the enablement rejections above. The underlying issue is the same: which structures would reasonably be expected to have the recited functional activity.

4. Claims 1-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Olsson, U.S. patent 5,073,540 or WO88/05784 (published 11 August 1988). Olsson disclose peptides useful as antagonists or agonists for membrane receptors. The prior art compounds have essentially the same structure as those of the instant application, see e.g. cols. 7 and 8. WO88/05784 discloses similar peptides, see e.g. claim 1. WO88/05784 also suggests modification of such peptides using conventional techniques to extent their biological halflives, see pages 21-23. Page 10 of the specification describes such conventional techniques.

It would have been prima facie obvious to one of ordinary skill in the art at the time of invention to modify the prior art peptides and to test functional activity on surface receptors or lymphocyte activity of the modified peptides using the assays disclosed in Olsson col.s 12-14 or by WO88/05784 on page 25. Further, page 40 of WO88/05784 explicitly suggests use of such peptides for prolonging graft survival time by reducing rejection cytolytic CTL activity.

Claims limited to products reasonably expected to retain the unexpected properties attributed to dimeric products, such as the dimer described in Table 1, would be free of this rejection. Applicant is encouraged to contact the Examiner telephonically to discuss this issue.

--Applicant urges that there was no motivation in the prior art to produce dimers. However, one with ordinary skill in the art would at least expect that dimers of the same unit would exert the same functional effects as a monomer. It is noted that the claim language is not limited to palindromic dimers--e.g. (aa79-84)-(aa84-79). Claim 1 encompasses α-β dimers that "may be the same or different". Thus, dimers such as (aa79-84)-(aa79-84) are NOT excluded from the language of claim 1. The prior art rejection is maintained for alpha-alpha dimers, but not for dimers containing a reverse "beta" sequence.

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thomas M. Cunningham, Ph.D, J.D. whose telephone number is (703) 308-3968. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

TC

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GROUP 1800